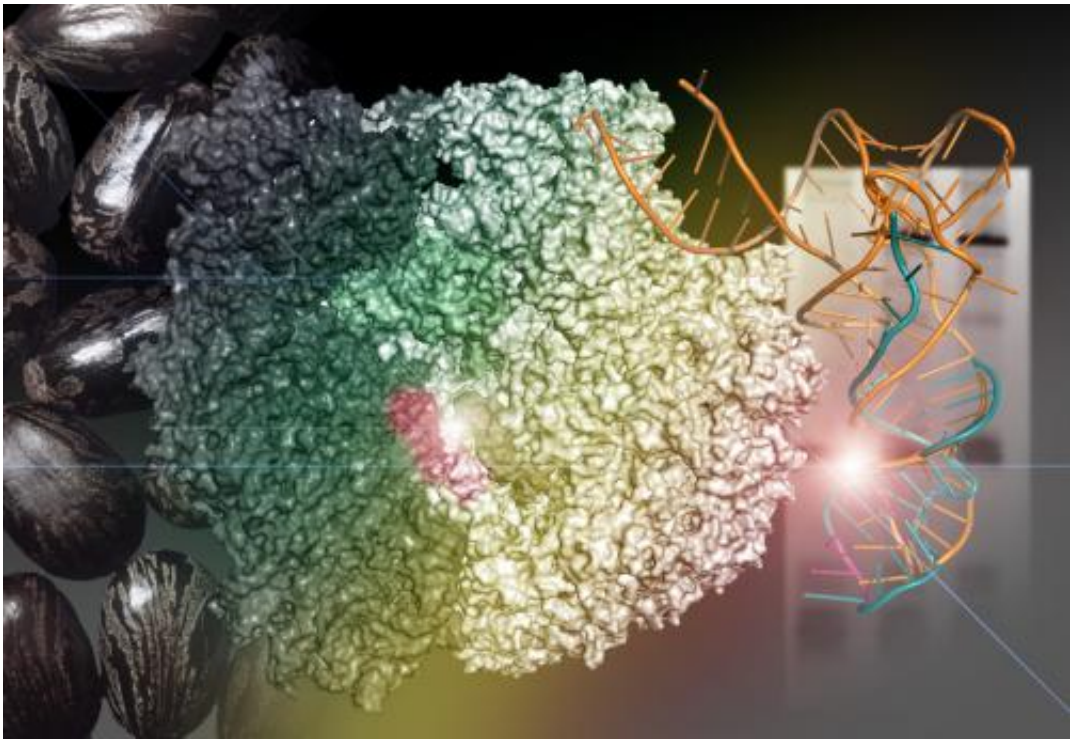
Bacteria use lethal cytotoxins to evade antibiotic treatment

November 18 2013



The figure shows the bacterial 70S ribosome with the cleavage point for the cytotoxin VapC20 marked with red. To the right is transfer RNA, which is cleaved by a similar mechanism in the pathogenic organism *Shigella flexneri*. Behind this is an RNA gel showing the actual cleavage reaction in the ribosome. Credit: Ditlev E. Brodersen

In spite of the fact that the first antibiotics were discovered almost a century ago, infectious diseases such as tuberculosis, encephalitis and

meningitis are still serious diseases for humans in the twenty-first century. The World Health Organization (WHO) estimates that there are more than 8 million new cases of tuberculosis per year on a global scale, and that more than 300,000 of these are due to multidrug-resistant strains that are not only difficult to treat, but are also emerging rapidly in regions such as Eastern Europe.

Bacterial tolerance is not just due to resistance, but also to the formation of persistent cells that have gone into a dormant state where they are no longer sensitive to antibiotics. On the molecular level, this process is controlled by a number of advanced cytotoxins produced by the bacteria themselves in order to survive. In Mycobacterium tuberculosis – the organism that causes tuberculosis – there are no fewer than 88 such toxins, all of which presumably help the organism to survive.

In a new article in the renowned journal *Nature Communications*, an international team of researchers with the participation of the Department of Molecular Biology and Genetics, Aarhus University, has revealed the mechanism behind one of these toxins – VapC20. It turns out that when the toxin is activated, it destroys the tuberculosis bacteria's own protein 'factory' (the ribosome) by cleavage. The bacteria are thereby unable to produce proteins in the short term, and thus avoid the effect of antibiotics that also often attack the ribosome.

When treatment with antibiotics is completed, the pathogenic bacteria 'wake up' and are ready to synthesise new ribosomes. Surprisingly, it appears that the location in the ribosome that is cleaved by VapC20 is the same place that is destroyed by the strong cytotoxins α-sarcin and ricin, which are found in plants such as castor beans and are twice as venomous as cobra snake poison.

Further analysis of the cleavage point in the ribosome also shows that the mechanism is presumably general for a number of the many toxins, and

the new knowledge could therefore be used in future to develop new ways of treating pathogenic bacteria by impairing their ability to use such cytotoxins.

More information: Winther, KS, Brodersen, DE, Brown, AK, and Gerdes, K (2013) VapC20 of Mycobacterium tuberculosis Cleaves the Sarcin Ricin Loop of 23S rRNA, *Nature Communications*. www.nature.com/ncomms/2013/131 … full/ncomms3796.html

Provided by Aarhus University